PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK2004/000599	10.09.2004	11.09.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/26, G01N33/74, G01N33/72, A61P3/10

Applicant
NOVO NORDISK A/S

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/DK2004/000599

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ *in computer readable form*

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ *In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto* has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the *entire international application*,

☒ claims Nos. 1-29

because:

☒ the said international application, or the said claims Nos. 1-29 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	30-46
	No:	Claims	1-29, 54-58
Inventive step (IS)	Yes:	Claims	30-46
	No:	Claims	1-29, 54-58
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	see separate sheet

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Concerning section III:

Claims 1-29, 54-58 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Concerning section IV:

This Authority considers that there are 3 inventions covered by the claims indicated as follows:

Group 1: Claims 1-29, 54-58
Use of GLP-1 agonists in the treatment of patients newly diagnosed with type 1 diabetes.

Group 2: Claims 30-46
Diagnosis/monitoring the outcome of type 1 diabetes by analysing the concentration of endogenous GLP-1(7-37) and GLP-1(7-36) amide.

Group 3: Claims 47-53
Diagnosis/monitoring the outcome of type 1 diabetes by analysing the level of HbA_{1c}.

The groups of inventions are not unitary a priori because there is no technical relationship between them: group 1 relates to the treatment of patients newly diagnosed with type 1 diabetes whereas group 2 relates to the monitoring of the evolution of the disease in patients which have already developed type 1 diabetes and are under GLP-1 treatment.
In addition, the aim of administering GLP-1 agonists has no common technical feature with the aim of evaluating endogenous GLP-1 or HbA_{1c} level.
Hence the inventions of groups 1 and 2 are not so linked as to form a single general inventive concept and do not meet the requirements of Rule 13.1 & 2 PCT.

The groups 2 and 3 of inventions are also not unitary a posteriori because the diagnosis of type 1 diabetes by measuring the level of HbA_{1c} is well known in the art, see the documents cited in the search report. Hence the two solutions to the problem of providing alternative diagnostic means of type I diabetes, on the one hand measuring the level of endogenous GLP-1, and on the other hand measuring the level of HbA_{1c}, are not so linked as to form a common inventive concept.

The examination is carried out for those claimed which have been the subject of a search, i.e. claims 1-58

Concerning section V:

1. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

   D1: WO 95/31214 A (LONDON HEALTH ASS ; DUPRE JOHN (CA)) 23 November 1995 (1995-11-23)
   D2: WO 00/42026 A (CORNELIS DE JONG JOHANNES ; KODRA JANOS TIBOR (DK); PETTERSON INGRID V) 20 July 2000 (2000-07-20)
   D3: WO 03/002136 A (NOVO NORDISK AS) 9 January 2003 (2003-01-09)
   D4: WO 98/08871 A (NOVONORDISK AS ; KNUDSEN LISELOTTE BJERRE (DK); NIELSEN PER FRANKLIN () 5 March 1998 (1998-03-05)
   D5: US-A-5 424 286 (ENG JOHN) 13 June 1995 (1995-06-13)
   D6: WO 2004/050115 A (NOVO NORDISK AS) 17 June 2004 (2004-06-17)
   D7: EP-A-0 201 187 (NOVO INDUSTRI A/S; NOVO NORDISK A/S) 12 November 1986 (1986-11-12)
   D8: OLSEN BIRTHE SUSSANE ET AL: "A 6-year nationwide cohort study of glycaemic control in young people with Type 1 diabetes: Risk markers for the development of retinopathy, nephropathy, and neuropathy" JOURNAL OF DIABETES AND ITS COMPLICATIONS, vol. 14, no. 6, November 2000 (2000-11), pages 295-300, XP002319816 ISSN: 1056-8727

D9: DANNE T ET AL: "Persistent differences among centers over 3 years in glycemic control and hypoglycemia in a study of 3,805 children and adolescents with type 1 diabetes from the Hvidore Study Group." DIABETES CARE. AUG 2001, vol. 24, no. 8, August 2001 (2001-08), pages 1342-1347, XP002319817 ISSN: 0149-5992

D10: HOEY H ET AL: "Good metabolic control is associated with better quality of life in 2,101 adolescents with type 1 diabetes." DIABETES CARE. NOV 2001, vol. 24, no. 11, November 2001 (2001-11), pages 1923-1928, XP002319818 ISSN: 0149-5992

D11: NORDLY S ET AL: "Quality of diabetes management in children and adolescents in Denmark." DIABETIC MEDICINE : A JOURNAL OF THE BRITISH DIABETIC ASSOCIATION. JUL 2003, vol. 20, no. 7, July 2003 (2003-07), pages 568-574, XP002319819 ISSN: 0742-3071

D12: VILSBOELL T ET AL: "EVALUATION OF BETA-CELL SECRETORY CAPACITY USING GLUCAGON-LIKE PEPTIDE 1" DIABETES CARE, AMERICAN DIABETES ASSOCIATION, ALEXANDRIA, VA, US, vol. 23, no. 6, June 2000 (2000-06), pages 807-812, XP000984497 ISSN: 0149-5992

Unless indicated otherwise reference is made to the relevant passages emphasized in the search report.

2. Group 1

2.1 *Preliminary remark:* The feature in independent claim 1 of the patient being "newly diagnosed with type 1 diabetes when the GLP-1 agonist is first administered to said patient" is so unclear that it cannot be taken into consideration for evaluating novelty *(see section VIII)*. It follows that this feature is not understood and cannot establish novelty as it is impossible to evaluate what is really meant by it. The same objection applies to the subject-matter of claims 2-6 and 15.

2.2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-29 and 54-58 is not new in the sense of Article 33(2) PCT:

The document D1 discloses the combined use of insulin and GLP-1(7-37) or GLP-1(7-36)amide in the treatment of type 1 diabetic patients. Therefore D3 anticipates the subject-matter of claims 1-18, 27-29, 54-58.

The document D2 discloses the use of non-peptide GLP-1 agonists combined with insulin in the treatment of type 1 diabetes, thereby anticipating the subject-matter of claims 1-17 and 27-29, 54-58.

The documents D3 and D4 disclose the use of GLP-1 agonists, e.g. Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37), in the treatment of type 1 diabetes. Hence they anticipate the subject-matter of claims 1-6, 10-23, 27-29, 54-58.

The document D5 discloses the use of exendin-3 or -4 in the treatment of diabetes type 1, thereby anticipating the subject-matter of claims 1-6, 10-17, 24-29, 54-58.

2.3 In view of the outstanding novelty objection regarding all claims of group 1, it is not possible at present to draft an opinion regarding inventive activity of these claims.

3. Group 2

Claims 30-46 pertain to the diagnosis of type I diabetes, in particular to the diagnosis of the evolution of the disease (claims 30-43) and to the pertinence of GLP-1 agonist administration (claims 44-46), by the determination of the endogenous concentration of GLP-1 (7-37) and GLP-1 (7-36) amide in a sample.
None of the available prior art dicloses a link between endogenous GLP-1 (7-37) and GLP-1 (7-36) amide, and the decrease in beta cell function, i.e. the evolution of type I diabetes.
Hence the subject-matter of claims 30-46 appears to be novel and inventive.

4. Group 3

Claims 47-53 pertain to the diagnosis of type I diabetes (and the subsequent decision

to administer a GLP-1 agonist) by the determination of the level of HbA_{1c}. These claims appear to be a mere reformulation of the practice of the art (D7-D11) where the correlation between level of HbA_{1c} and type I diabetes evolution is well-known and well-described. Presently it does not appear that the subject-matter of claims 47-53 comprise any new technical feature over the practice of the art, hence these claims are not consider as being novel.

5. For the assessment of the present claims 1-29, 54-58 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Concerning section VI

The document WO 2004/050115 A (NOVO NORDISK AS) published on 17 June 2004 might be relevant for assessing novelty in the regional phases as it discloses the use of exendins in the treatment of type 1 diabetes.

Concerning section VIII

The feature in independent claim 1 of the patient being "newly diagnosed with type 1 diabetes when the GLP-1 agonist is first administered to said patient" is unclear, hence the subject-matter of claim 1 does not meet the requirements of Art. 6 PCT. Indeed, according to claims 7, 12 to 14 and to the description p. 5, lines 1-10 and 18-30, "newly diagnosed patients" encompass patients having been treated by insulin for a certain period of time before GLP-1 is administered. The patients may even be in remission, which implies that a first insulin treatment has taken place and the insulin dose required is decreased.